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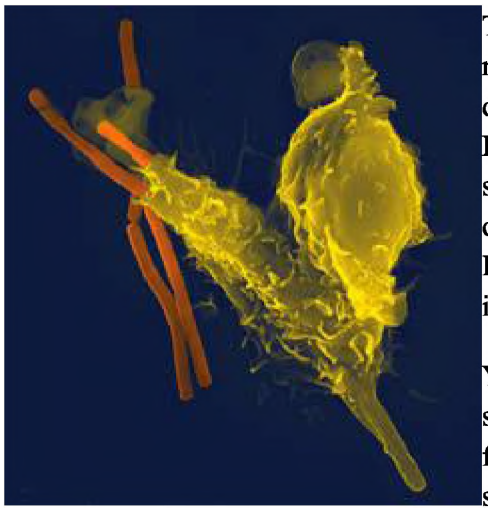
Studies show how unchecked alarms and undiscerning defenders spark autoimmune disease



To protect the peace you need to know how to identify the enemy or dangerous misunderstandings can arise. Over 50 million Americans suffer from autoimmune diseases and the attacks they spark from the body's own defenses. Dr. Cynthia Leifer, immunologist at the Cornell University College of Veterinary Medicine, studies the checks and balances keeping our immune defenses from spinning out of control. Her latest paper in the August 2011 issue of the European Journal of Immunology adds to a growing map of how these mechanisms can work or fail, illuminating possible pathways for therapies to counter autoimmune disease.

Your immune system has two kinds of troops: the adaptive immune system's specialized intelligence forces and the innate immune infantry fighting first on the front lines. While adaptive T-cells and B-cells run background checks to identify specific invaders and devise specially-tailored attacks, the quicker innate immune cells begin the defense based on more general intruder recognition.

"Innate immune cells have an internal watchdog called 'Toll-Like Receptor 9' (TLR-9) that set off the alarm whenever it encounters DNA," said Leifer. "Our paper describes a novel regulatory mechanism that keeps TLR-9 from responding to a person's own DNA and initiating autoimmunity. The receptor undergoes proteolytic cleavage, a protein-chopping process that separates the part of TLR-9 that binds to DNA from the part that signals the immune cell to respond."

Proteolytic cleveage happens more in normal cells than in infected cells, keeping the alarms quiet when there is no infection to fight.
"By cutting the connection and preventing these signals we are protected from dangerous inflammatory responses." said Leifer. "Therefore, we believe this may be a key regulatory mechanism that could fail in autoimmune disease patients, and a potential path for therapies designed to help quiet those alarms."

This finding is the latest in a series from Leifer's lab mapping how TLR-9 works and how it might fail in autoimmune disorders. Their first pivotal discovery, published in the Journal of Immunology in 2004, showed how defective receptors mistake self-cells for intruders when exposed to the self's DNA. Such glitches have been implicated in autoimmune diseases involving numerous DNA-hunting antibodies, including rheumatoid arthritis and systemic lupus erythematosus

(lupus), a painful and sometimes fatal chronic disorder that causes vivid rashes and affects as many as 1.5 million Americans.

"Innate immune cells can determine whether a cell is a virus, bacterium, or protozoan, or part of the self," said Leifer. "They use receptors that recognize generic classifying patterns, but sometimes those patterns exist in both microbes and your own cells."

So why don't receptors responding to patterns shared by both sides normally attack the host?

"Despite depending on such a universal trigger as DNA, TLR-9 doesn't usually react to the self," said Leifer. "We are mapping the critical regulatory mechanisms preventing this and how they might fail in autoimmune disorders."

While most cells keep their receptors on the cell surface, Leifer showed that innate immune cells prevent recognition errors by keeping TLR-9 indoors.
"An innate immune cell eats microbes it encounters by pulling them into an intracellular stomach where TLR-9 lives," said Leifer. "Digestion releases the microbes' DNA and the receptor triggers a response. If TLR-9 lived on the cell surface, any time your tissue was damaged its DNA could into the extracellular environment, reach the receptor, and trigger an immune response. So we keep these receptors inside where they only see DNA from microbes the immune cells consume."

In a 2006 issue of the Journal of Biological Chemistry, Leifer described the protein sequences in TLR-9 that act as address labels guiding where the receptor ships within a cell. Her current work explores what happens when it gets lost in transit.

"We chop up and mutate the receptor to see what happens when defects deliver it wrongly," said Leifer. "If TLR-9 goes to the cell surface and reacts to host DNA by inducing autoimmune symptoms, this may indicate which mechanisms and defects lead to lupus and similar diseases."

This growing map of regulatory mechanisms guiding innate immune responses may help guide future therapies that could help immune systems distinguish between self and other and quiet overzealous responses to alleviate autoimmune attacks.